

## Relation between Blood Lead Levels and Childhood Anemia in India

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Lead pollution is a substantial problem in developing countries such as India. The US Centers for Disease Control and Prevention has defined an elevated blood lead level in children as  $\geq 10$   $\mu\text{g/dl}$ , on the basis of neurologic toxicity. The US Environmental Protection Agency suggests a threshold lead level of 20–40  $\mu\text{g/dl}$  for risk of childhood anemia, but there is little information relating lead levels  $< 40$   $\mu\text{g/dl}$  to anemia. Therefore, the authors examined the association between lead levels as low as 10  $\mu\text{g/dl}$  and anemia in Indian children under 3 years of age. Anemia was divided into categories of mild (hemoglobin level 10–10.9 g/dl), moderate (hemoglobin level 8–9.9 g/dl), and severe (hemoglobin level  $< 8$  g/dl). Lead levels  $< 10$   $\mu\text{g/dl}$  were detected in 568 children (53%), whereas 413 (38%) had lead levels  $\geq 10$ –19.9  $\mu\text{g/dl}$  and 97 (9%) had levels  $\geq 20$   $\mu\text{g/dl}$ . After adjustment for child's age, duration of breastfeeding, standard of living, parent's education, father's occupation, maternal anemia, and number of children in the immediate family, children with lead levels  $\geq 10$   $\mu\text{g/dl}$  were 1.3 (95% confidence interval: 1.0, 1.7) times as likely to have moderate anemia as children with lead levels  $< 10$   $\mu\text{g/dl}$ . Similarly, the odds ratio for severe anemia was 1.7 (95% confidence interval: 1.1, 2.6). Health agencies in India should note the association of elevated blood lead levels with anemia and make further efforts to curb lead pollution and childhood anemia.

anemia; child; India; lead; lead poisoning

Abbreviation: CI, confidence interval.

Environmental lead exposure occurs from automobile exhaust in areas of the world where leaded gasoline is still being used and from drinking water in areas where lead pipes are being used. Exposure at home may occur because of ingestion of old leaded paint or of pigments and glazes used in pottery (1). Careless disposal of products containing lead may contaminate soil, particularly in urban areas. Elevated lead levels in the body have been associated with renal and cardiovascular disease, hematologic toxicity, and irreversible neurologic damage (1). After measures to control lead pollution were undertaken in the United States,

beginning in 1970, blood lead levels in children declined by more than 80 percent (1). However, in developing countries such as India, control of lead pollution has been much slower and more sporadic. Previous studies have estimated that more than half the children in India have blood lead levels  $\geq 10$   $\mu\text{g/dl}$  (2, 3).

Anemia in children is also a substantial problem in India (4, 5) and leads to increased morbidity and mortality (6, 7). Adverse health effects of anemia in children include impaired psychomotor development and renal tubular function, poor cognitive performance, and mental

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retardation (8–13). The association of lead toxicity with anemia in children has been explored in the past, primarily in populations at high risk, such as children living near a lead smelter (14, 15). Because of the high prevalence of lead pollution in India and the hazardous consequences of anemia, information linking these factors would be invaluable for informing Indian government authorities and international public health agencies about the extent and public health implications of lead pollution and anemia in India.

The 1998–1999 Indian National Family Health Survey was the first study to provide information on blood lead levels of children under 3 years of age in two major Indian metropolitan areas (Mumbai and Delhi) (16, 17). In agreement with earlier studies (2, 3), the National Family Health Survey found that approximately 50 percent of children in Mumbai and 45 percent in Delhi had blood lead levels  $\geq 10$   $\mu\text{g/dl}$ . Information regarding the proportion of children with mild or moderate anemia by blood lead level was also provided (16, 17). These proportions were similar for both metropolitan areas. However, the causes of anemia in India are multifactorial, and the National Family Health Survey did not explore the relation of increased anemia risk to elevated blood lead level by anemia severity, accounting for sociodemographic, economic, and other confounding factors.

Although the US Centers for Disease Control and Prevention has defined an elevated blood lead level as a level  $\geq 10$   $\mu\text{g/dl}$ , primarily on the basis of its neurologic toxicity (18), the US Environmental Protection Agency suggests a threshold level of 20–40  $\mu\text{g/dl}$  for anemia in children (1, 19, 20). There is little information regarding the relation between lead levels  $< 40$   $\mu\text{g/dl}$  and anemia in children. We hypothesized that after controlling for potential confounders, blood lead levels  $\geq 10$   $\mu\text{g/dl}$  would be associated with a higher risk of anemia of varying severity in comparison with levels  $< 10$   $\mu\text{g/dl}$ .

## MATERIALS AND METHODS

### Database description

The National Family Health Survey was conducted with support from the US Agency for International Development and the United Nations Children's Fund (21). The survey was carried out to assess population health and nutrition in India. The National Family Health Survey included a sample of approximately 90,000 ever-married women aged 15–49 years from all 26 states of India (22). These women completed a structured interview to provide information regarding their families and their living conditions. Informed consent to include a child in the study was obtained from the child's mother in the metropolitan areas of Mumbai (Bombay) and Delhi. Mothers were asked whether blood samples could be collected from children aged  $< 3$  years for measurement of blood lead and hemoglobin levels. Of the 1,082 children for whom blood lead levels were measured, three with missing information on hemoglobin level and one with a hemoglobin value of 0.8 g/dl were excluded from the

study. Only 106 children in the study were from families with two or more children. Database validation was performed by field editors and field supervisors, and data were verified further during processing. Approval for this study was obtained from the institutional review boards of the relevant institutions.

### Outcome measures

Anemia was defined according to the World Health Organization's criteria of a hemoglobin level  $< 11$  g/dl in children (23). It was further classified into categories of mild (hemoglobin level 10–10.9 g/dl), moderate (hemoglobin level 8–9.9 g/dl), and severe (hemoglobin level  $< 8$  g/dl) anemia. Hemoglobin was measured in the field using a portable HemoCue system (HemoCue, Inc., Angelholm, Sweden). The child's hand or foot was first thoroughly washed with soap and water. A single drop of blood from a finger prick (or heel prick in the case of infants) was drawn into a cuvette, which was then inserted into the instrument.

### Measurement of exposure

Free treatment was offered for any child with a blood lead level  $\geq 45$   $\mu\text{g/dl}$ . After the hemoglobin measurement was obtained, 2–3 drops of blood from the same site were mixed with a treatment reagent and transferred to a sensor by pipette. The sensor was then introduced into a LeadCare analyzer (LeadCare, Inc., Chelmsford, Massachusetts), which displayed the results. The All India Institute of Medical Sciences (New Delhi, India) and the Industrial Toxicology Research Center (Lucknow, India) verified the accuracy of the LeadCare analyzer.

### Statistical analysis

The National Family Health Survey provided data on the relations of sociodemographic, economic, and other variables with anemia and blood lead levels (16, 17). We performed chi-square tests or *t* tests to compare population characteristics (including sociodemographic and economic factors) with the presence of anemia and lead levels. Variables that were statistically significant at the 0.1 level in comparisons of baseline population characteristics with lead levels or significantly independently associated with elevated lead levels were included as confounders in multivariate regression models. A standard of living index (22) was calculated by assigning an index score to each household based on socioeconomic characteristics (house type, toilet facility, source of lighting, main fuel used for cooking, source of drinking water, presence of a separate room for cooking, home ownership, and ownership of agricultural land, irrigated land, livestock, and durable goods). Standard-of-living index scores were 0–14 for a low standard of living, 15–24 for an intermediate standard, and 25–67 for a high standard. Lead levels were considered as  $< 10$   $\mu\text{g/dl}$  and  $\geq 10$   $\mu\text{g/dl}$ , and in some models as  $\geq 10$ –19.9  $\mu\text{g/dl}$  and  $\geq 20$   $\mu\text{g/dl}$ . There were few children with values of  $\geq 40$   $\mu\text{g/dl}$ , and analyses were conducted both

**TABLE 1. Relation of selected baseline characteristics to blood lead levels in children under 3 years of age, Mumbai (Bombay) and New Delhi metropolitan areas, India, 1998–1999**

	Blood lead level			
	<10 µg/dl (n = 568)		≥10 µg/dl (n = 510)	
	No.	%	No.	%
Age (months)*				
Mean (standard deviation)	16.3 (10.5)		20.2 (9.2)	
Missing data	5	0.9	1	0.2
Religion				
Hindu	415	73.1	358	70.2
Muslim	113	19.9	111	21.8
Christian	10	1.8	7	1.4
Sikh	14	2.5	13	2.6
Other/no religion	12	2.1	20	3.9
Missing data	4	0.7	1	0.2
Social class†				
Higher caste	369	65.0	323	63.3
Scheduled caste/scheduled tribe	102	18.0	104	20.4
Other backward caste	97	17.1	83	16.3
Standard of living index*				
Low	13	2.3	35	6.9
Intermediate	228	40.1	248	48.6
High	302	53.2	201	39.4
Missing data	25	4.4	26	5.1
Place of residence				
Slum household†	152	26.8	167	32.8
Not a slum household	75	13.2	60	11.8
Missing data	341	60.0	283	55.5
Breastfeeding*				
Currently breastfeeding	359	63.2	296	58.0
Duration of breast-feeding (months)‡				
0–6	64	11.3	59	11.6
7–12	66	11.6	70	13.7
13–24	59	10.4	79	15.5
25–36	7	1.2	3	0.6
Missing data	13	2.3	3	0.6
Mother's education*				
Some education	458	80.6	363	71.2
No education	110	19.4	147	28.8

Table continues

**TABLE 1. Continued**

	Blood lead level			
	<10 µg/dl (n = 568)		≥10 µg/dl (n = 510)	
	No.	%	No.	%
Father's educational level*				
No education	48	8.5	55	10.8
Primary school	59	10.4	66	12.9
Secondary school	255	44.9	252	49.4
Higher than secondary school	204	35.9	136	26.7
Missing data	2	0.4	1	0.2
Mother's occupation				
Not employed	499	87.9	443	86.9
Agricultural work	2	0.4	3	0.6
Other (nonagricultural) work	48	8.5	51	10.0
Missing data	19	3.4	13	2.6
Father's occupation				
Not employed	14	2.5	14	2.8
Agricultural work	10	1.8	7	1.4
Other (nonagricultural) work	203	35.7	158	31.0
Skilled/unskilled manual work	271	47.7	257	50.4
Missing data	70	12.3	74	14.5
No. of children in immediate family*				
≤2	377	66.4	292	57.3
3–5	173	30.5	186	36.5
>5	18	3.2	32	6.3
Mother's anemia status				
No anemia (hemoglobin level ≥12 g/dl)	296	52.1	241	47.3
Anemia (hemoglobin level <12 g/dl)	269	47.4	269	52.8
Missing data	3	0.5	0	0.0
Source of drinking water				
Piped	515	90.7	459	90.0
Hand pump	44	7.8	48	9.4
Well	1	0.2	0	0.0
Other	8	1.4	3	0.6
Total	568	52.7	510	47.3

\*  $p \leq 0.05$  (Pearson chi-square test or  $t$  test for comparison between categories of variables).

† Scheduled caste/scheduled tribe, other backward caste, and living in a slum household are indicators of lower socioeconomic status in India.

‡ Not currently breastfeeding.

including and excluding these children. Generalized ordered logistic regression (24) analysis was carried out for assessment of associations between the four categories of anemia (with no anemia as the reference group) and lead levels (with

<10 µg/dl as the reference group). Wald tests for the equality of odds ratios obtained from generalized ordered logistic regression analysis were performed. Statistical analyses were conducted using Intercooled Stata for Windows (version 8.0;

**TABLE 2. Relation of anemia with category of blood lead level in children under 3 years of age, Mumbai (Bombay) and New Delhi metropolitan areas, India, 1998–1999\***

Anemia category (hemoglobin level)	Blood lead level					
	<10 µg/dl (n = 568)		10–19.9 µg/dl (n = 413)		≥20 µg/dl (n = 97)	
	No.	%	No.	%	No.	%
No anemia (≥11 g/dl)	185	32.6	100	24.2	26	26.8
Mild (10–10.9 g/dl)	143	25.2	97	23.5	21	21.7
Moderate (8–9.9 g/dl)	198	34.9	165	40.0	35	36.1
Severe (<8 g/dl)	42	7.4	51	12.4	15	15.5

\*  $p \leq 0.001$  (Jonckheere-Terpstra test).

Stata Corporation, College Station, Texas) and SAS for Windows (version 8.02; SAS Institute, Inc., Cary, North Carolina).

## RESULTS

Approximately 47 percent of the children had blood lead levels  $\geq 10$  µg/dl (38 percent between 10 µg/dl and 19.9 µg/dl, 9 percent  $\geq 20$  µg/dl, and 0.3 percent  $\geq 40$  µg/dl; maximal value, 46.7 µg/dl). Most of the children studied were Hindu, in a proportion similar to that in the entire Indian population. Lead levels  $\geq 10$  µg/dl were significantly associated with increasing age, duration of breastfeeding, a lower standard of living index, a lower parental educational status, and a greater number of siblings ( $p < 0.05$ ). Most of the mothers were not employed, and the proportions of fathers engaged in skilled or unskilled manual work were similar across lead levels, although 14 percent had missing values. Source of drinking water was not significantly related to lead levels (table 1).

The prevalence of anemia by blood lead level (<10 µg/dl, 10–19.9 µg/dl, and  $\geq 20$  µg/dl) was cross-tabulated with anemia severity (table 2). A significantly greater proportion of children with lead levels  $\geq 10$  µg/dl (75.3 percent) had anemia as compared with children with lead levels <10 µg/dl (67.4 percent). The differences were greatest for moderate anemia (39 percent for lead levels  $\geq 10$  µg/dl and 35 percent for lead levels <10 µg/dl;  $p = 0.1$ ) and severe anemia (13 percent for lead levels  $\geq 10$  µg/dl and 7 percent for lead levels <10 µg/dl;  $p = 0.002$ ). In addition, significantly greater proportions of children with lead levels  $\geq 10$ –19.9 µg/dl and  $\geq 20$  µg/dl had severe anemia as compared with children with lead levels <10 µg/dl ( $p < 0.05$ ). We carried out the Jonckheere-Terpstra test (25, 26) to determine whether the ordered anemia outcomes were identically distributed in the three ordered categories of lead level (in table 2). We obtained a  $p$  value less than 0.001, which implies a systematic change in outcome with change in lead level.

The unadjusted and adjusted odds ratios for mild, moderate, and severe anemia are presented in table 3, based on comparisons of lead levels <10 µg/dl with levels  $\geq 10$  µg/dl. Since the proportional odds assumption did not

**TABLE 3. Relation between elevated ( $\geq 10$  µg/dl) blood lead levels and anemia in children under 3 years of age, Mumbai (Bombay) and New Delhi metropolitan areas, India, 1998–1999†**

Anemia category (hemoglobin level)	Unadjusted OR‡	95% CI‡	Adjusted§ OR	95% CI
Mild (10–10.9 g/dl)	1.5	1.1, 1.9	1.2	0.9, 1.7
Moderate (8–9.9 g/dl)	1.5	1.2, 1.9	1.3*	1.0, 1.7
Severe (<8 g/dl)	1.9	1.2, 2.8	1.7**	1.1, 2.6

\*  $p \leq 0.05$ ; \*\*  $p = 0.02$ .

† Odds ratios were obtained by means of generalized logistic regression analysis using “no anemia” as the reference category.

‡ OR, odds ratio; CI, confidence interval.

§ Adjusted for age of the child (in months), duration of breastfeeding, number of children in the immediate family, mother’s education, maternal anemia, father’s educational level, father’s occupation (indicator variables were used for missing values), and standard of living index ( $n = 1,003$  in the final adjusted models).

hold true, we used generalized ordered logistic regression models (which relax the proportional odds assumption) to calculate these odds ratios. The adjusted models were controlled for age of the child, duration of breastfeeding, number of children in the immediate family, mother’s education, maternal anemia, father’s education, father’s occupation, and standard of living index. The greatest association with lead level was observed for severe anemia, whereas mild anemia was not significantly associated with lead level. Tests for equality of the three odds ratios were not statistically significant. We obtained similar results when children with lead levels  $\geq 40$  µg/dl were excluded. When we considered incremental lead levels with levels <10 µg/dl used as the reference category, the odds ratios for moderate and severe anemia were 1.4 (95 percent confidence interval (CI): 1.0, 1.8) and 1.7 (95 percent CI: 1.1, 2.7), respectively, for lead levels  $\geq 10$ –19.9 µg/dl, and 1.1 (95 percent CI: 0.7, 1.7) and 1.8 (95 percent CI: 0.9, 3.6), respectively, for lead levels  $\geq 20$  µg/dl.

We conducted a sensitivity analysis including only the youngest child from each household to test for possible clustering of children within households. Thus, the 106 children from households with two or more children were excluded. After controlling for potential confounders, we obtained odds ratios of 1.4 (95 percent CI: 1.1, 1.8) for moderate anemia and 1.8 (95 percent CI: 1.1, 2.9) for severe anemia.

We also studied whether hemoglobin level had a negative linear dose-response relation with lead level using scatter plots, but we did not find a linear or log-linear decline. This is in agreement with previous studies (15).

## DISCUSSION

Approximately half of the children in this study had blood lead levels  $\geq 10$  µg/dl, which is similar to previous estimates made for children in India (2, 3). The cutoff value of 10 µg/dl is significant, because it is the Centers for Disease Control and Prevention’s defined limit for an elevated lead level,

primarily based on neurologic toxicity (18). In this study, after accounting for other factors influencing anemia, blood lead levels  $\geq 10$   $\mu\text{g/dl}$ , including values  $\geq 10$ – $19.9$   $\mu\text{g/dl}$ , were significantly associated with moderate and severe anemia. The adjusted odds ratios were only modestly lower than the unadjusted values, which suggests that there was little confounding by age of the child, duration of breast-feeding, number of children in the family, mother's and father's educational status and occupation, maternal anemia, and standard of living index.

Schwartz et al. (15) used data from 579 children living near a primary lead smelter in the US state of Idaho to demonstrate that blood lead levels near 25  $\mu\text{g/dl}$  were associated with anemia in a dose-related manner. Lead levels of 40–60  $\mu\text{g/dl}$  and  $>60$   $\mu\text{g/dl}$  were associated with 18 percent and 40 percent probabilities of anemia, respectively, in children aged 1 year. However, few children ( $n = 20$ ) with lead levels  $<20$   $\mu\text{g/dl}$  were studied. Drossos et al. (27) reported that children with blood lead levels  $\geq 30$   $\mu\text{g/dl}$  had a linear decline in hemoglobin level. That study included only 15 children with lead levels  $<19$   $\mu\text{g/dl}$  (27). Landrigan et al. (14) reported a significant negative relation between blood lead level and hematocrit value at lead levels  $\geq 80$   $\mu\text{g/dl}$ . Froom et al. (28) suggested that hemoglobin levels did not correlate well with blood lead levels and suggested further that anemia is not related to lead at low blood lead levels. Other studies have reported a variable association (29–33). The Environmental Protection Agency has suggested a threshold lead level of 20–40  $\mu\text{g/dl}$  for a decrease in hemoglobin in children, although a clear cutoff is not defined. Our study demonstrates a significant association of moderate and severe anemia with blood lead levels, even in the range of 10–19.9  $\mu\text{g/dl}$ . Although it was not statistically significant, the odds ratio for mild anemia was also elevated.

Lead causes anemia by impairment of heme synthesis and an increased rate of red blood cell destruction (34). On the other hand, it is also possible that iron deficiency, which is a proven cause of anemia, leads to increased absorption of lead in the body, resulting in high blood lead levels (35–38), but this association has been refuted in some studies (39–42). Although a causal pathway cannot be determined from our study, our findings clearly demonstrate an association between varying severity of anemia and elevated blood lead levels.

We would like to acknowledge the limitations of our study. The lead values were based on field capillary blood testing; they were not confirmed for accuracy in a laboratory (43), although these values have been found to be closely related (44). The prevalence of anemia, especially anemia due to iron deficiency, is very high in developing countries such as India, and we may not have directly considered all confounding factors. However, we controlled for factors closely associated with other causes of anemia in the multivariable regression models.

The high proportion of children with blood lead levels  $\geq 10$   $\mu\text{g/dl}$  in Mumbai and Delhi and the association of elevated lead levels with anemia should be given immediate attention by the Indian government, as well as other global agencies. An elevated lead level, because of its association with anemia and other toxic effects per se, could have hazardous health and economic consequences in children

(1, 14, 45, 46). Although the government of India recently phased out the use of leaded gasoline, efforts to control overall lead pollution remain inadequate. Lead pollution from other sources such as paint, industrial processes, cosmetics, and medicines should be controlled. The beneficial effects of aggressive lead pollution control can be seen in data from the United States. Between 1976 and 1980, 88 percent of US children aged 1–5 years had lead levels  $\geq 10$   $\mu\text{g/dl}$ . This prevalence has steadily declined, to 9 percent in 1988–1991, 4 percent in 1991–1994, and 2 percent in 1999–2000 (47). Measures for preventing and treating anemia in Indian children, such as control of anemia in mothers during pregnancy, iron supplementation, and malaria prevention (48), should also be undertaken.

In summary, in this study, relatively low blood lead levels in children were significantly associated with elevated risk of moderate and severe anemia. Since lead pollution can be controlled and steps can be taken to reduce the prevalence of childhood anemia, regulatory and health agencies in India should consider this a priority and make more substantial efforts toward resolving these public health problems.

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